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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/007,574	11/09/2001	Cesare Peschle	9855-26U3	3808

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EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 03/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/007,574	PESCHLE, CESARE	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,32,46,50 and 54* is/are pending in the application.

4a) Of the above claim(s) *12,18,32,50 and 54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-17 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 1/29/04 is acknowledged.
1-18, 32, 46, 50 and 54 are pending.

Claims 12, 18, 32, 50 and 54 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Claims 1-11, 13-17 and 46 are under consideration in the instant application.

2. The filing date of the instant claims is deemed to be the filing date of the instant applications, i.e. 11/09/2001, as the parent application 09/322,352 does not support the claimed method of generating a differentiated human cell of a selected type, comprising maintaining an isolated human KDR^+ stem cell in the presence of a differentiated mammalian cell of the selected type, the limitations of the instant application. If applicants disagree, applicants should present a detailed analysis as to why the claimed subject matter has clear support in the parent application.

3. Applicant's submission of a product brochures from Sigma-Aldrich Corporation as evidence that KDR1 and KDR2 antibody are commercially available has obviated the previous rejection of claim 11 under 35 U.S.C. 112 first paragraph regarding the deposit issue.

In view of the amendment, filed 1/29/04, the following rejections remain:

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-11, 13-17 and 46 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.
The Specification does not reasonably provide enablement for a method of generating a differentiated human cell of a selected type , the method comprising maintaining an isolated human KDR+ stem cell in the presence of a differentiated any mammalian cell of the selected type as claimed in claims 1-11 and 13-17 or maintaining an isolated human KDR+ stem cell in a medium conditioned to reflect the presence of differentiated mammalian cells of the selected

type, as claimed in claim 46. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action, mailed on 08/26/03.

Applicant's arguments, filed 1/29/04 have been fully considered, but have not been found convincing.

Applicant asserts that : (i) it is not relevant to the enablement how homogenous is the population of post-natal $CD34^+$ KDR^+ cells. The Specification very clearly lays out how to isolate $CD34^+$ KDR^+ cells; (ii) Examples 2, 4 and 5 of the specification demonstrate that post-natal $CD34^+$ KDR^+ cells are capable of differentiation into endothelial cells.

Contrary to Applicant's assertion it is the examiner position that it is relevant for the enablement how homogenous is the initial population of post-natal $CD34^+$ KDR^+ cells . Moreover, the issue raised in the previous Office Action was not how to isolate post-natal $CD34^+$ KDR^+ cells. The examiner agrees that the methods for isolating said population was well known in the art at the time the invention was made.
However, as was stated in the previous Office Action, it is not clear from the specification how homogeneous is the population of natal CD34+KDR+ primitive stem cell that give rise to both hematopoietic and stromal stem cell population. There is no disclososure on how homologeneous is this cell population (e.g. 90%, 95% or 99%). It is very possible that the cell population contain heterogeneous cell population that give rise to both hemopoietic and stromal elements. What was the sensitivity of the method for selecting natal CD34+KDR+ primitive stem cell, what is the accurate and reproducible quantification of such selection. One skilled in the art would not know the homogeneous nature of the natal CD34+KDR+ primitive stem cell using the teaching of the specification alone. Moreover, Waoller et al. (Blood, 1995, v.85, pages 2422-2435) teach that there is no solid evidence for a hypothesis of a "common stem cell" (see page 2422 in particular). Based on the analysis of over 30,000 stem cells with a variety of CD34+ phenotypes and 864 stromal culture , Waoller et al. concluded that the is no evidence that a single cell can differentiate along both a hematopoietic and stromal lineage (see page 2434 in particular). In addition, Holden et al. (Science, 2002, V.296, pages 2126-2129) teach that thre is no evidence that purified blood stem cells can contribute to any other tissue (see page 2127 in particular).
It is also not clear from the Specification how it was asserted that the injected human donor post natal CD34+KDR+ cells differentiated into any specific cell type as claimed in claim 17. There is no characterization of these cells as to phenotype or functional capacity. It is possible that these cells are an irrelevant contamination of the stem cells selection process or do not provide function associated with stromal microenvironment. Moreover, there is no evidence from the Specification that there was no fusion of the $CD34^+KDR^+$ cells with cells of the other lineages. Holden et al. (Science, 2002, V.296, pages 2126-2129) teach that cells can mutate and develop markers characteristics of other lineages or that cells injected into a foreign tissue can take up local DNA and thus appears to have changes identity (see page 2126 in particular). Moreover, Holden et al. further teach that fusion scare has given further impetus to effort to establish

rigorous standards for demonstrating plasticity such as: the cells must be properly identified at the outset, because a single alien cell in ostensibly purified culture could produce misleading results. The cells must contribute to the function of the host tissue. There is no indication that demonstrate functionality of said cells in the specification.

With regards to Examples 2 , 4 and 5 of the current Specification.

It is noted that the data of the Example 2 clearly demonstrated that *in vitro* post natal $CD34^{+}KDR^{+}$ are capable of differentiation into cells at sequential stages of differentiation that shows the cell markers of endothelial cells. However, this experiment was done at very specific serum-free liquid suspension culture, without the presence of : (i) a differentiated mammalian cell of the selected type or (ii) a medium conditioned to reflect the presence of differentiated mammalian cells of the selected type, as claimed in the instant claims. The mere fact that stem cells *in vitro* are capable for differentiation was well known at the time of the invention. In the examples 4 and 5 the post natal CD34+KDR+ cells were injected in non-immunocompromised murine blastocytes and the fate of the injected human cells during murine embriogenesis and post-natal life was followed (see Example 4 of the Specification as filed) or injected into the regenerating muscle (see Example 5 of the Specification in particular).

However, the issue raised in the previous Office Action was that that the specification does not teach how to extrapolate data obtained from above discussed limited studies to the development of effective *in vivo or in vitro* methods of generating a differentiated human cell of a specific selected type, such as the recited in claim 17, wherein isolated human KDR+ stem cells are maintained in the presence of any differentiated mammalian cell or in a medium conditioned to reflect the presence of any differentiated mammalian cells, whereby the stem cell differentiated to become the differentiated human cell of the selected type, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of a methods of generating a differentiated human cell of a specific selected type, such as recited in claim17, wherein isolated human KDR+ stem cells are maintained in the presence of any differentiated mammalian cell or in a medium conditioned to reflect the presence of any differentiated mammalian cells, whereby the stem cell differentiated to become the differentiated human cell of the selected type.

Thus the specification fails to demonstrate that isolated human KDR+ stem cells can be generated to differentiate into any differentiated human cell by maintaining an isolated human KDR+ stem cell in the presence of a differentiated mammalian cell of the selected type as claimed in claims 1-11 and 13-17 or maintaining an isolated human KDR+ stem cell in a medium conditioned to reflect the presence of differentiated mammalian cells of the selected type, as claimed in claim 46 and the art does not recognize that a single cell can differentiate along both a hematopoietic and stromal lineage. The courts have held that it is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. (Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001).

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method of generating a differentiated human cell of a selected type , the method comprising maintaining an isolated human KDR+ stem cell in the presence of a differentiated any mammalian cell of the selected type as claimed in claims 1-11 and 13-17 or maintaining an isolated human KDR+ stem cell in a medium conditioned to reflect the presence of differentiated mammalian cells of the selected type, as claimed in claim 46 wherein the stem cell is separated from the differentiated mammalian cell by *any* porous barrier , as claimed in claim 4. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

6. Claims 5-9, stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action, mailed on 08/26/03.

Applicant's arguments, filed 1/29/04 have been fully considered, but have not been found convincing.

Applicant is not in possession of a method of generating a differentiated human cell of a selected type , the method comprising maintaining an isolated human KDR+ stem cell in the presence of a differentiated any mammalian cell of the selected type as claimed in claims 5-9 wherein the stem cell is isolated from a human hematopoietic tissue using *any* reagent that specifically binds with KDR.

Applicant asserted that : (i) the only claim that recite a reagent is claims 5 and 10 and thus the rejection is not applicable to claims 6-9; (ii) the application provides sufficient written description of "reagent that specifically binds to KDR .

Contrary to Applicant's assertion, it is noted that since claims 6-9 are dependent claims of the base claim 5 the rejection of is applicable to all dependent claims.

The specification fails to describe *any* reagent other then antibody, that specifically binds with KDR. Applicant has disclosed a limited number of species; therefore, the skilled artisan cannot envision all the contemplated possibilities recited in the instant claims. Consequently, conception in either case cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequences themselves are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

A description of a genus of reagent that specifically binds with KDR may be achieved by means of a recitation of a representative number of reagents falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

8. Claims 1-11, 13-17 and 46 rejected under 35 U.S.C. 103(a) as being unpatentable over Bruder et al (US Paten NO:5,736396) in view of Lemischka (US Patent 5,912133) and as evidenced by the Specification disclosure on page 63, lines 4-8 and page 4, lines 4-10 for the same reasons set forth in the previous Office Action, mailed on 08/26/03.
Applicant's arguments, filed 1/29/04 have been fully considered, but have not been found convincing.

Applicant asserts that: (i) US Patent '396 does not teach or suggest use of human KDR^+ stem cells for induction; (ii) US Patent '133 does not teach or suggest that FLK-1 receptor bearing cells can be used in a method of generating human cell of specific type; (iii) the is no suggestion to combine the teaching of US Patent '396 and US Patent '133.

Applicants have traversed the primary and the secondary references pointing to the differences between the claims and the disclosure in each reference. Applicant is respectfully reminded that the rejection is under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. see In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981) See MPEP 2145. This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968). The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and not is it that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). See MPEP 2145.

In response to applicant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992). The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144

In this case, US Patent '396 teaches a method of generating a differentiated cell of a selected type by incubation human mesenchymal stem cells in the presence of differentiated mammalian cells or condition medium that are effective to induce differentiation into a lineage of choice.(see entire document, Abstract , Column 1, lines 50-55 and Fig.1 in particular). US Patent '396 teaches that human mesenchymal stem cells can be isolated from various tissues that contained stem cells (see column 4 , lines 10-65 in particular). US Patent '396 teaches that human mesenchymal stem cells can be either injected at the site of skeletal defects or incubated in the presence of differentiated cells (see column 5, lines 11-20 in particular).

US Patent '396 does not teach that stem cells are human KDR^+ stem cells.
US Patent '133 teaches a method of isolating human FLK^+ stem cells using antibody that specifically binds FLK-1 (see entire document, Abstract in particular). The Specification on

page 63, lines 4-8 disclosed that human KDR^+ stem cells are the same subpopulation of $CD34^+$ of cells as human FLK^+ stem cells. US Patent '133 teaches that human FLK^+ stem cells can be obtained from various tissues that contained stem cells (see column 14, lines 20-50). US Patent '133 teaches that isolated human FLK^+ stem cells have an ability to differentiate *in vitro* or *in vivo*. This ability has an important therapeutic applications (see overlapping column 7 and 8 in particular).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent '133 to those of US Patent '396 and substitute isolated human mesenchymal stem cells to isolating human KDR^+ stem cells to obtain a claimed method of generating a differentiated human cell of a selected type comprising maintaining an isolated KDR+ stem cells in the presence of a differentiated mammalian cells of the selected type.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because isolated human KDR^+ stem cells can be induced to differentiate *in vitro* or *in vivo* and this ability has an important therapeutic applications as taught by US Patent '133 . This subpopulation of human stem cells can be used to generated a differentiated human cell of a selected type by the method taught by US Patent '396 .

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim 4 is included because this functional limitation would be an obvious variation of the method using a condition media taught by US Patent '396. It will be immediately obvious to one skill in the art that the use a porous barrier, having pores of a size sufficient to allow the passage of a small proteins but not stem cells as claimed in claim 4 will result in obtaining a condition medium as taught by US Patent '396. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum conditions involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

Claims 6-10 are included because it would be conventional and within the skill of the art to identify various tissues that contained KDR^+ stem cells and used KDR1 and KDR2 antibody that were known and readily available to a person of ordinary skill in the art at the time the invention was made (see Applicant's arguments, filed 1/29/04, page 8 in particular) . In addition, Applicant himself acknowledge that any tissue that contains stem cells can be used (see page 4, line 4-10 of the instant Specification in particular). Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges or conditions involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

Claims 14-16 are included because it would be obvious , conventional and within the skill of the art to use differentiated mammalian cells of different origin, since US Patent '396 teaches a method of generating a differentiated cell of into a lineage of choice. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges or conditions involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

9. No claim is allowed

10. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/ 272-0840 The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/ 272-0841 .

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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